REMARKS

Applicants respectfully request entry of amendments to claims 1, 3, 4, 8, 9, 12, 13, 23, 25, 26, 36, 38, and 80-81. Support for the amendments can be found throughout the specification, including page 1, paragraph [0004], page 9, paragraph [0025], page 11, paragraph [0033], page 21, paragraph [0067], and the originally filed claims and, therefore, do not add new matter.

Applicants submit that pending claims 1, 3-9, 12, 13, 23, 25, 26, 36, 38, 48, and 80-81 are in condition for allowance, or are in better condition for presentation on appeal, and respectfully request that the claims as amended be entered.

Rejection Under 35 U.S.C. §112, Second Paragraph

Claims 1, 3-9, 11-13, 23, 25-26, 36, 38, 44, 48, and 78-81 stand rejected under 35 U.S.C. §112, second paragraph, as allegedly being indefinite. As claims 11, 44, 78, and 79 have been canceled, the rejection as applied to these claims is rendered moot.

Applicants traverse the rejection, including as it might apply to the amended claims, for the reasons given below.

The claims no longer recite "one primer binds to a sequence of SEQ ID NO: 22 and SEQ ID NO: 23" so the rejection is rendered moot. Applicants have amended the claims to recite "the first and/or second primer is complementary to a consensus region between SEQ ID NO:22 and SEQ ID NO:23, and wherein such first and second primers or probes flank non-consensus regions between SEQ ID NO:22 and SEQ ID NO:23." The terms "complementary," "consensus," and "non-consensus" are terms of art and would be known to one of skill in the art generally as 1) a sequence in an oligonucleotide or polynucleotide chain in which the bases are able to form base pairs with a sequence of base pairs in another oligonucleotide or polynucleotide chain (complementary) and 2) residues that represent nucleotides that occur in common at each position in a sequence (consensus). The terms are recited on page 11, paragraph [0033] and page 4, paragraph [0013] of the instant application. As such, one of skill in the art would understand the metes and bounds of the terms.

For these reasons, Applicants respectfully request that the rejection be withdrawn.

Rejections Under 35 U.S.C. §112, First Paragraph

Claims 1, 3-9, 11-13, 23, 25, 26, 36, 38, 44, 48, and 78-81 stand rejected under 35 U.S.C. §112, first paragraph as allegedly lacking written description support. As claims 11, 44, 78, and 79 have been canceled, the rejection as applied to these claims is rendered moot.

Applicants traverse the rejection, including as it might apply to the amended claims, for the reasons given below.

The Office Action alleges, in pertinent part, that 1) as the claims recite SEQ ID NOs: 22 and 23, the sequence identifiers encompass full length genes and cDNAs that are not described; 2) as the claims are broadly drawn to canine amelogenin, it is intimated that such claims embrace species beyond the scope of the disclosure based on potential combinations between canines and the number of canines in the genus; and 3) no guidance is provided to detect differences between the X and Y chromosomes. Further, the Action alleges that in view of factors recited (e.g., partial structure of the DNAs, claim breadth, and lack of correlation between structure and function of the gene at issue, including the knowledge level of the skilled artisan), one of skill in the art would not recognize from the disclosure that Applicants were in possession of the genus of DNAs which comprise SEQ ID NO: 22 and 23. Applicants respectfully submit that such allegations are incorrect.

Notwithstanding the amended claims, it is not clear as to how the Action has come to this position given the fact that at the time the invention was filed, a BLAST search of the dog genome (referenced at page 6, paragraph [0019], "The Dog Genome: Survey Sequencing and Comparative Analysis," Kirkness et al. (2003) Science, Vol 301:1898-1903) using either or both of SEQ ID NO: 22 or SEQ ID NO: 23 would show, at minimum, 1) that the sequences align with a sex chromosome to an extent greater than would be expected at random; 2) the pattern of alignment for each sequence is unique (e.g., SEQ ID NO:22 shows 100% identity with one specific region of the X chromosome and neither SEQ ID NO: 22 nor SEQ ID NO:23 align with any other non sex-chromosome); and 3) if the characterized dog genome in the Kirkness et al. reference is providing the *typical* dog genome for the scientific community (i.e., those of skill in

the pertinent art), such a showing should be representative for *all* breeds to which the characterized genome applies (i.e., canis familiaris).

Since the characterized dog genome of Kirkness et al. does represent, as purported, the genome *typical of all breeds* within canis familiaris,[1] and the sequences as recited in the present disclosure align only with a sex chromosome identified in this genome (see, e.g., Exhibits A and B), the skilled artisan would appreciate, at minimum, that *SEQ ID NOs: 22 and 23 are useful in identifying sex chromosomes in all breeds of dogs which fall under the typical dog as represented by that genome* (i.e., the scope of the method as claimed). And to insist that the breadth of the claims would not include those breeds for which the genome data is representative (i.e., "[t]he domestic dog species (*Canis familiaris*) includes more than 400 breeds"[2]), is to ignore the value of such information to one of skill in the art (i.e., disregards the knowledge base of the skilled artisan).

Nevertheless, the position taken in the Office Action in view of the present claims is inapposite in that the scope of the claims would not encompass full-length genes and cDNAs that are not described. For example, the instant claims recite primers or probes which are complementary to a consensus sequence of SEQ ID NO:22 and SEQ ID NO:23, where these primers or probes flank non-consensus sequences. As such, the scope of the primers and probes includes those sequences which embrace the identifiers that are useful in identifying non-consensus sequences associated with the X chromosome (e.g., residues 45-54 [**TGC**TATGCCC] of SEQ ID NO:22) or Y chromosome (e.g., residues 45-54 [**CAG**TATGCC**T**] of SEQ ID NO:23) as disclosed in the specification (i.e., as can bee seen in the alignment of FIG. 5). For example such probes or primers include, but are not limited to, SEQ ID NOs: 3, 4, and 5. Whether such primers and probes can be used to identify a full length canine amelogenin sequence or cDNA (a property which in fact they do possess) is irrelevant to the argument on claim scope. That such sequences can be used to practice the claimed method is what Applicants

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[1] See, also, < http://www.ncbi.nlm.nih.gov/projects/genome/guide/dog/ >, last visited, December 28, 2005.

[2] See, e.g., <http://www.ncbi.nlm.nih.gov/books/bv.fcgi?rid=coffeebrk.chapter.643>, last visited, December 28, 2005.

claim to be in possession of, and as stated above, one of skill in the art would recognize such possession given the localized alignment data evidence as illustrated in the Exhibits (e.g., sex-linked) and in view of the genomic data available at the time of filing.

Regarding the element "canine amelogenin," the claims recite the gene as a *target* of the primers or probes which are complementary to SEQ ID NO:22 and or SEQ ID NO:23. The amelogenin gene is defined and well known in the art, as evidenced by the recitations in the Action (e.g., the stating of a specific GenBank accession number at page 5, line 18, and selected information from the Tachi et al. and Asano et al. references). Further, as stated above, the claimed sequences for amelogenin is shown to align with a sex chromosome on the typical dog genome to an extent greater than would be expected at random (see, e.g., Exhibits A and B); 2) the pattern of alignment for each sequence is unique (see, e.g., Exhibits A and B); and 3) as the characterized dog genome as referenced was generated to provide the *typical* dog genome to those of skill in the pertinent art, such a showing should be representative for *all* breeds to which the characterized genome applies (i.e., canis familiaris).

Regarding guidance to detect differences between the X and Y chromosomes, the specification clearly describes 1) gender primer design (e.g., at page 29, paragraphs [0098]-[0099]); 2) a specific set of reaction and PCR conditions for gender marker identification (e.g., at page 31, paragraph [0105]), including modifications thereof, for the purpose, for example, to fit the primers in a microsatellite multiplex assay (e.g., at page 30, paragraph [0101]); and 3) illustrative results using such conditions as described (Figures 1-5), including, at page 22, paragraph [0070], the statement that "gender was tested with these primers in over **10,000 dog samples**, and in **all** of these assays, **gender was correctly identified**." (Emphasis added).

As such, one of skill in the art could envision the binding of the claimed primer/probe sequences to the well-known, well-defined, art-recognized target (i.e., amelogenin) or specifically recited sequence identifiers, and would appreciate that the inventors were in possession of the genus of primers/probes at the time the invention was filed to practice the invention as claimed. That is all that is required.

For these reasons, Applicants respectfully request that the rejection be withdrawn.

Claims 1, 3-9, 11-13, 23, 25-26, 36, 38, 44, 48, and 78-81 stand rejected under 35 U.S.C. §112, first paragraph, as allegedly lacking enablement. As claims 11, 44, 78, and 79 have been canceled, the rejection as applied to these claims is rendered moot.

Applicants traverse the rejection, including as it might apply to the amended claims for the reasons given below.

The Office Action alleges, in pertinent part, that as the claims are broadly drawn to canine amelogenin, the gene encompasses species outside of the scope of the disclosure, and further, because of the number of breeds of domestic dogs, no guidance is provided to the skilled artisan to detect differences between amelogenin genes on X and Y chromosomes, even for canis familiaris species. The Action also alleges that as the alignment data is unclear, one of skill in the art could not distinguish whether non-consensus sequences are informative in the absence of specific sample information (e.g., number of animals used, specific breeds, etc). The Action further alleges that as probes bind to both the X and Y chromosomes, such probes would not allow for determination of gender since hybridization to both genders is allowed. Moreover, the Action suggests that because of alleged variability between species and breeds, detection of differences to establish gender could not be predicted given such variability, and thus undue experimentation would be required for the skilled artisan to practice the full scope of the invention. Applicants respectfully submit that such allegations are incorrect.

While it is appropriate to recognize variability in determining the scope of invention, determination of what is needed to support generic claims to biological subject matter depends on a variety of factors including 1) knowledge in the particular field, 2) the extent and content of the prior art, 3) the maturity of the science or technology, and 4) the predictability of the aspect at issue. Capon v. Eshhar, 76 U.S.P.Q.2d 1078, 1084, 418 F.3d 1349, at 1356 (Fed. Cir. 2005).

As stated above, the knowledge in the field and the extent and content of the prior art is certainly exemplified in "The Dog Genome: Survey Sequencing and Comparative Analysis," Kirkness et al. (2003) Science, Vol 301:1898-1903, as referenced at page 6, paragraph [0019]. Since the characterized dog genome of Kirkness et al. represents the genome *typical of all breeds* within canis familiaris, and the sequences as recited in the present disclosure align only with a sex chromosome identified in this genome (see, e.g., Exhibits A and B), the generic claims are

supported because one of skill in the art would predict that all breeds of dogs which fall under the typical dog as represented by that genome would show substantially identical alignment for the amelogenin gene sequences as disclosed. As such, the species recited, in view of the gene as disclosed, does not fall outside of the scope of the disclosure for this reason.

Regarding the alignment data, as supported by Exhibits A and B, because SEQ ID NO:22 is 100% identical to the region of the canis familiaris X chromosome identified as similar to Rho-GTPase activating protein 6[3] and SEQ ID NO:23 is only 79% identical to the same region, together with the fact that neither bind to any other non sex-chromosome (i.e., BLAST analysis demonstrates that all other chromosomes are excluded), one of skill in the art would recognize that the non-consensus regions are present only on the X or Y chromosome. Thus, as offered in the Action "the ordinary artisan would be able to detect differences using this guidance." (See page 13, first paragraph, of the Action). Further, because the specification provides methods for identifying non-consensus sequences (i.e., by hybridization, sequencing, and/or number/size differentiation of PCR products), including which non-consensus sequences are associated with each X and Y chromosome, guidance is provided to the skilled artisan to detect differences between amelogenin gene sequences (i.e., SEQ ID NO:22 and SEQ ID NO:23) on X and Y chromosomes for canis familiaris species. Moreover, at minimum, given the alignment data, the specification provides enough guidance to determine whether a sample contains nucleic acids which are homologous to the canine amelogenin sequences as recited in the present disclosure.

Thus, the present invention represents more than "a mere germ of an idea," because the specification supplies the novel aspects of the invention (i.e., detection of non-consensus sequences which are specific to either the X or Y chromosome), and detection of sequence differences by hybridization or amplification to ascertain gender using selected sequences is certainly not in the early stages of development (e.g., page 1, paragraph [0004]). (See, also, Genentech, Inc. v. Novo Nordisk, 42 U.S.P.Q.2d 101, 108 F.3d 1361 (Fed. Cir. 1997)). Further,

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[3] Amelogenin has been shown to be within the first intron of rho GTPase-activating protein (rhoGAP) gene named *ARHGAP6* in humans (Xp22.3). Prakash et al., Functional analysis of ARHGAP6, a novel GTPase-activating protein for RhoA. Human Mol Gen (2000) 9(4):477-488.

in the present specification, not only are the general teachings of how to select the requisite probes or primers disclosed (e.g., page 27, paragraph [0090] to page 28, paragraph [0091]; page 29, paragraph [0097] to page 30, paragraph [0101]; Tables 1-7; and FIG. 5), but also specific examples are provided showing the successful use of the probes/primers in the method as claimed (e.g., page 29, paragraph [0100] to page 31, paragraph [0105], and FIGS. 1-4, including that gender has been tested using these primers in over 10,000 dog samples from a wide range of breeds, and in all of these assays, gender was correctly identified: paragraph [0070]). Moreover, standardized description and identification of sequences, including known conditions for hybridization and PCR, are disclosed (e.g., page 17, paragraph [0034] to paragraph [0035]; page 15, paragraph [0045] to page 17, paragraph [0048]; page 20, paragraph [0061] to page 25, paragraph [0080]; and page 27, paragraph [0089] to page 34, paragraph [0114]). And while such procedures involve some level of technical manipulation, because such methods and steps are routinely used in the art, such procedures do not rise to the level of undue experimentation. (See, e.g., Johns Hopkins University v. Cellpro, Inc., 47 U.S.P.Q.2d 1705, 152 F.3d 1342 (Fed. Cir. 1998), where the court stated that "experimentation does not constitute undue experimentation" where "it is merely routine.").

Regarding unpredictability, it is not necessary that every permutation within a generally operable invention be effective in order for an inventor to obtain a generic claim, provided that the effect is sufficiently demonstrated to characterize the generic invention. See, e.g., In re Angstadt, 537 F.2d 498, 504 (CCPA 1976). Accordingly, generic inventions are not *per se* invalid because success for each possible iteration is not assured. Capon, at 1357.

Respectfully, the probes/primers of the claimed method bind to complementary sequences based on SEQ ID NO:22 and SEQ ID NO:23. That they bind to the consensus sequences on both the X and Y chromosome does not, *per se*, make the invention non-enabled. As recited in the claims, and as presented in the specification (e.g., Table 1), the complementary probes/primers allow for the non-consensus sequences to be distinguished. Because the probes/primers flank such non-consensus regions, various products can be obtained, where the presence of these products correlates with gender. For example, using a set of such primers (e.g., BKF90052/BKF0059 and/or BKF90055/ BKF0065), PCR products from both males and females

generate a 143 base product, while males produce an additional 146 base product (see, page 29, paragraph [0100] to page 30, paragraph [0101]). These products would be predicted directly from Table 1, Table 3, and FIG. 5. Further, these results are consistent (see, e.g., page 30, last sentence in paragraph [0100]), including results from a further study conducted with 74 dog samples (34 female and 40 males), using the assay methods and primers as described, where the assay results in a single PCR product of approximately 140 bases in females (corresponding to the X chromosome) and two PCR products of approximately 140 bases and 142 bases in males (corresponding to the Y chromosome). In this study, gender was determined correctly in 100% of the samples (see, Item 3 in the **Declaration of Applicants Under 37 C.F.R §1.132**).

Moreover, research was conducted, *inter alia*, to further test the robustness of the assay using methods and primers as described (see, Exhibit C of the **Declaration**). The Exhibit shows the number of dogs (125,037) and breeds used (231) in the analysis. From this analysis the error call rate; i.e., where the gender genotyped is opposite of that reported by the owner, was determined to be 1.6% (i.e., 1,996/125,037). In addition, there were no database errors detected (i.e., no single allele in females was detected where that allele corresponded to "Y" instead of "X"). This data provides further support for the teachings of the instant application, where using the methods and primers disclosed, as filed, accurately and precisely determines gender in a wide range of breeds.

Regarding the Wands factors, 1) While the invention is in the biological arts, as stated above, it is not necessary that every permutation within a generally operable invention be effective in order for an inventor to obtain a generic claim, provided that the effect is sufficiently demonstrated to characterize the generic invention. See, e.g., In re Angstadt, 537 F.2d 498, 504 (CCPA 1976). For the present set of facts, products associated with each gender were obtained as predicted from the disclosure, and such products were obtained consistently; 2) The unpredictability as allegedly supported by the cited references is no longer valid in view of Kirkness et al. (2003) Science, Vol 301:1898-1903, further, the number of successful applications of the method as recited in the specification (i.e., working examples) is **10,000**; 3) Regarding guidance, as stated above, one of skill in the art would recognize that the non-consensus regions are present only on the X or Y chromosome (all other chromosomes being

excluded). Thus, as offered in the Action at page 13, "the ordinary artisan would be able to detect differences using this guidance."; 4) Regarding quantity of experimentation, such as design of appropriate consensus primers to flank non-consensus regions, development of conditions for hybridization or PCR, etc., these procedures are merely routine (e.g., see Example 1, at page 27, paragraph [0089] to page 31, paragraph [0107]), and do not rise to the level of undue experimentation; and 5) Regarding the level of skill in the art (i.e., high), such a skilled artisan would have the knowledge and capabilities of using the information provided in the specification (i.e., design appropriate consensus primers to flank non-consensus sequences, develop conditions for hybridization or PCR, etc.) to make and use the invention commensurate in scope with the amended claims.

Therefore, the claims are enabled because the specification provides appropriate guidance, working examples, and prediction of success based on observed results using the claimed method such that one of ordinary skill in the art could practice the invention as claimed, in the absence of undue experimentation.

For these reasons, Applicants respectfully request that the rejection, including as it may be applied to the amended claims, be withdrawn.

Conclusion

Applicants submit that pending claims 1, 3-9, 12, 13, 23, 25, 26, 36, 38, 48, and 80-81 are in condition for allowance, or are in better condition for appeal. The Examiner is invited to contact Applicants' undersigned representative if there are any questions relating to this submission.

No fee is deemed necessary with the filing of this paper. However, the Commissioner is hereby authorized to charge any fees required by this submission, or credit any overpayments, to Deposit Account No. 07-1896 referencing the above-identified docket number. A duplicate copy the Transmittal Sheet is enclosed.

Respectfully submitted,

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